REMARKS

Reconsideration of this application is respectfully requested. Claims 1-58 are pending. Claims 9, 10, 21-27, 31-40 and 43-58 have been withdrawn from consideration as drawn to a non-elected group. Claims 1-8, 11-20, 28-30, 41 and 42 are currently at issue. Invention Group I has been elected with further election of the species 2-(2-methylthiazol-4-yl)ethynylpyridine (MTEP).

Rejections under 35 U.S.C. § 103(a) for obviousness

The Examiner has maintained the rejection of claims 1-8, 11-20, 28-30, 41 and 42 as allegedly being obvious over WO 2001/16121 to Cosford *et al.* ("Cosford") in view of Bonney *et al.* (1997) "Bladder Dysfunction in Schizophrenia," *Schizophrenia Research* 25:243-49 ("Bonney") and Nilvebrandt (2001) "Clinical Experiences with Tolterodine," *Life Sciences* 68:2549-56 ("Nilvebrandt"). This is the only outstanding rejection.

The Examiner states that Bonney "clearly teaches the association of urinary incontinence in patients suffering from Schizophrenia," and contends that Bonney teaches the neurobiological and pathophysiological similarities between schizophrenia and urinary incontinence. The Examiner further states that since Cosford teaches the claimed MTEP compound for the treatment of schizophrenia, that Bonney "raises the reasonable expectation that the MTEP compound would be administered to a patient suffering from urinary incontinence associated with schizophrenia," and further that "if the same compound is administered to a subject suffering from, or with a strong likelihood of suffering from, the same condition as claimed ... then whatever effect such a compound has in treating urinary incontinence must necessarily be present" (emphasis added). The Examiner points to M.P.E.P § 2112.

It is respectfully submitted that the Examiner's position is not well-taken: it is based on both a logical fallacy and a misunderstanding of the pertinent case law. The logical fallacy is that urinary incontinence has not been established in the prior art as being due to schizophrenia or vice versa, such that treatment of one condition would be likely to effect treatment of the other condition. The legal misunderstanding is that to show inherency, it is sufficient to establish a probability that a

certain event will coexist with another event. This is simply not true. We discuss both of these problems with the Examiner's position. In particular, we establish the following:

1) Bonney does not state that Schizophrenia is always accompanied by incontinence, just that the two co-exist a portion of the time.

2) Bonney does not provide any basis why Schizophrenia and incontinence would be treated by the same agent.

3) More important, Bonney states that incontinence was not treated when Schizophrenia was treated with antipsychotic medication.

4) Additionally, Bonney does not teach that all antipsychotic medications have the same mode of action, such that if one of them treats urinary incontinence others will similarly treat incontinence, even when they have great disparities in structure.

5) On the contrary, applicants have adduced evidence that at least one anti-schizophrenic drug, dozapine, causes urinary incontinence, which contradicts any speculation that such drugs would treat urinary incontinence.

The Bonney Reference Does Not Inherently Disclose Treatment of Urinary Incontinence in Schizophrenic Patients.

The terms "reasonable expectation" and "strong likelihood" are not found in the section of the M.P.E.P. to which the Examiner refers. Section 2112(IV) of the M.P.E.P. does direct:

> 'The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic' citing *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (emphasis added).

and further states that:

> 'In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that

the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art' citing *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original).

The Examiner acknowledges that incontinence is not an inherent characteristic of schizophrenia, stating "Bonney et al. clearly teaches the association of urinary incontinence in patients suffering from schizophrenia. Please see Bonney et al., page 246, Table 2," (See page 3, line 16-17 of the Final Office Action dated June 14, 2007) (emphasis added). The data referred to by the Examiner shows a 37% incidence of incontinence in schizophrenic patients, far below only that required for inherency which is 100%.

It is respectfully submitted that the Examiner has confused what must "necessarily" be present, *i.e.* the disorder, with the compound's ability to treat the disorder. In order for the "treatment of urinary incontinence" to be inherently present in Bonney, urinary incontinence must necessarily be present every time a patient is treated for schizophrenia in the disclosed study. It is not sufficient to assert that a schizophrenic patient is treated by the prior art compound based on the "likelihood" of concomitantly suffering from urinary incontinence 37% of the time. Nor is it sufficient to assert that it is "reasonable" to expect that a schizophrenic patient with urinary incontinence would be treated for urinary incontinence when administered the prior art compound. In other words, the disorder must necessarily be present when a patient is treated with a prior art compound. *Schering Corp. v. Geneva Pharms, Inc.*, 334 F.3d 1373, 1375 (Fed. Cir. 2003) (*citing Continental Can Co. v. Monsanto*, 948 F.2d 1264, 1268 (Fed. Cir. 1991).

The treatment of urinary incontinence with MTEP is not obvious because urinary incontinence is not necessarily present in schizophrenia patients. Therefore, a schizophrenic patient treated with the prior art compound, as disclosed by Cosford, did not necessarily lead to the treatment of urinary incontinence. This is because incontinence is not present in every schizophrenic patient, which is required to establish inherency. Therefore, the proper question is not whether any schizophrenic patient also suffered from urinary incontinence, but rather did every

schizophrenic patient also suffered from urinary incontinence. Inherency can only be shown when the patient populations are co-extensive. The Examiner has failed to cite a prior art reference that establishes that schizophrenia and urinary incontinence are disorders with coextensive patient populations. Bonney in fact proves that this is not the case as only 37% of the patients suffered from incontinence.

Bonney Does Not Explicitly Disclose Treatment of Urinary Incontinence and in Fact Teaches Away

The Examiner states that Bonney discloses that "the neurobiological and pathophysiological similarities between schizophrenia and urinary incontinence, such that the ventricular enlargement, neuronal loss with gliosis and dopamine dysregulation that occurs with schizophrenia subsequently interrupts the pathway of bladder control and, thus, results in urinary incontinence." However, this interpretation is incorrect. Instead, Bonney clearly discloses:

> This information prompted our group to postulate that schizophrenic urinary incontinence is neurogenic, caused by the upper central nervous system pathology documented above, and therefore a reflection of DH in some cases ... [t]he present study was designed to test the hypothesis that urinary incontinence and related symptoms are more prevalent in chronic schizophrenic patients than in a comparison group of comparably hospitalized patients with mood disorders. (*See* page 244, left column, ¶2-3 of Bonney) (emphasis added).

This quote is a far cry from establishment of an "association." It is instead pure speculation.

Bonney goes on to say:

> It was done with the clear understanding that subsequent studies would be needed to link these findings to brain pathology and urodynamic results and to exclude neuroleptic medication as a factor. It is beyond the scope of this paper

> to prove that the urinary symptoms of interest represent true neurogenic bladder dysfunction in every case because there was no opportunity to do urodynamic studies. (*See* page 244, left column, ¶3 of Bonney) (emphasis added).

This portion of Bonney establishes the preliminary nature of this study and the uncertainty of its speculation. Therefore, a person of ordinary skill in the art would not be motivated by its disclosure without the suggested further work being first carried out and actually yielding the speculated facts. It thus remains a fact that Bonney does not establish that Schizophrenia and incontinence are linked. Moreover, as shown below, Bonney fails to establish that anti-schizophrenic drugs are effective in treating incontinence, whether the incontinence was pathologically linked to Schizophrenia or not.

Bonney clearly teaches that schizophrenic patients undergoing treatment with schizophrenic drugs still suffer from urinary incontinence, stating:

> All patients took psychiatric medication during the year prior to interview. There were no consistent significant effects of any class of medication in relation to urinary incontinence of the three types studied ... Urinary incontinence was a persistent problem in both schizophrenia and mood disorder. Of 59 with urine leakage at any time, 50 (86%) still had the problem at interview. (*See* page 247, left column, ¶1 of Bonney) (emphasis added).

In our view, the foregoing indicates that anti-schizophrenic drugs are ineffectual for the treatment of urinary incontinence and teaches away from the use of anti-schizophrenic drugs to treat incontinence.

Some Known Anti-Schizophrenic Drugs Cause Urinary Incontinence

The Examiner further argues that in Applicants' previous response, no evidence was provided to establish that psychiatric medications contribute to incontinence, and further contends

that "generic allegations that 'psychiatric medications' as a general class contribute to urinary incontinence fails to establish any correlation between a specific species of drug ... and the induction of urinary incontinence in a patient."

It is respectfully submitted that at least one known schizophrenic drug, clozapine, is known to cause urinary incontinence. Attached are abstracts from five research papers, all published prior to the filing date of the present application, that describe the occurrence of urinary incontinence upon treatment with clozapine. These publications further support Bonney's own statements regarding the prevalence of urinary incontinence with the use of schizophrenic drugs ("It is notable that incontinence accompanies neuroleptic drug treatment (Ambrosini, 1984), which selectively blocks dopamine receptors in the basal ganglia (Gur and Pearlson, 1993),"(*See* page 248, left column, ¶3). These teachings, when taken alone, or combined with Bonney, teach away from the use of schizophrenic drugs for the treatment of urinary incontinence.

The Combination of Cosford, Bonney and Nilvebrandt Does Not Teach, or Make Obvious, the Present Claims

Finally, the Examiner states that it is not sufficient to argue that Nilvebrandt does not remedy the deficiencies of Cosford and Bonney, and that an appropriate response must "address the combined teachings as a whole." In the Office Action dated January 24, 2007, the Examiner states:

> One of ordinary skill in the art would have been motivated to combine the pharmaceutical composition of Cosford et al. with the muscarinic receptor antagonist tolterodine as taught by Nilvebrandt because each was known or recognized in the art to be useful for the same therapeutic purpose of treating urinary incontinence. The very fact that each was known in the prior art to have the same therapeutic utility raises the reasonable expectation of success that the two compositions, when combined, would have, at minimum, additive, if not synergistic, incontinence-ameliorating effects when combined. Page 8, ¶3 (emphasis added).

It is respectfully submitted that, as described above, Cosford does not teach the use of MTEP for the treatment of urinary incontinence. Therefore, it is untrue that "each" of Cosford and Nilvebrandt were known to be useful for the treatment of urinary incontinence as asserted by the Examiner. The drug of Cosford was not known nor suggested to be useful for the treatment of urinary incontinence. Therefore, there exists no motivation to combine these references. To the contrary, as outlined above, there are dys-motiviating teachings.

In addition, Nilvebrandt teaches only the use of tolterodine to treat overactive bladder and discloses no teaching, suggestion or motivation for the treatment of urinary incontinence by MTEP or any other mGlu5 receptor entagonist. Nor does Nilvebrandt disclose any teaching that can be combined with either Cosford or Bonney, or both, to achieve the invention as called for by the present claims.

For the foregoing reasons, Cosford, Bonney and Nilvebrandt do not make obvious claims 1-8, 11-20, 28-30, 41 and 42 of the present invention. The Examiner is therefore respectfully requested to withdraw the rejection of these claims for obviousness over the cited prior art.

In view of the preceding comments and amendments, the pending claims are believed to be in condition for allowance and such action is earnestly solicited.

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Respectfully submitted,

By
Adda C. Gogaris
Registration No.: 29,714
DARBY & DARBY P.C.
P.O. Box 770
Church Street Station
New York, New York 10008-0770
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant

1) Brain Res. 2001 May 18;901(1-2):219-29.

Clozapine inhibits micturition parameters and the external urethral sphincter during cystometry in anesthetized rats.

Vera PL, Nadelhaft I.

Department of Veterans Affairs Medical Center, R & D Service (151), Bay Pines, FL 33744, USA. pvera@hsc.usf.edu

Clozapine therapy has been associated with a high degree of urinary disturbances. The purpose of this study is to examine the effect of clozapine on urodynamic parameters and on the activity of the external urethral sphincter in anesthetized rats. Single cystometrograms (CMG) were performed on urethane-anesthetized female Sprague-Dawley rats, while also recording the EMG from the external urethral sphincter. Clozapine (0, 0.1, 1, 10 mg/kg) was administered intravenously. In addition, the peripheral end of the pudendal nerve was stimulated in order to determine if clozapine was exerting peripheral effects directly on the external urethral sphincter. Clozapine increased the bladder capacity while reducing the micturition volume thus resulting in a marked increase in the residual volume. The pressure threshold was increased but the peak pressure during contraction remained unchanged. **The expulsion time and contraction time were decreased and the amplitude of the high frequency oscillations (HFO) seen during the expulsion phase were markedly reduced and even abolished.** The EMG from the external urethral sphincter also showed marked decreases after clozapine, and the bursting pattern seen during HFO was abolished. Clozapine had no effect on the activity elicited from electrical stimulation of the pudendal nerve. **Clozapine inhibits several urodynamic parameters and inhibits the activity of the external urethral sphincter in anesthetized rats. These effects may help explain the urinary disturbances reported in the clinical literature.**

2) J Clin Psychiatry. 2000;61 Suppl 8:14-7; discussion 18-9.

Review and management of clozapine side effects.

Miller DD.

Department of Psychiatry, University of Iowa, Iowa City 52242-1057, USA.

Clozapine has demonstrated superior efficacy in relieving positive and negative symptoms in treatment-resistant schizophrenic patients; unlike other antipsychotics, it causes minimal extrapyramidal side effects (EPS) and has little effect on serum prolactin. Despite these benefits, the use of clozapine has been limited because of infrequent but serious side effects, the most notable being agranulocytosis. In recent years, however, mandatory blood monitoring has significantly reduced both the incidence of agranulocytosis and its associated mortality. The occurrence of seizures appears to be dose-related and can generally be managed by reduction in clozapine dosage. Less serious and more common side effects of clozapine including sedation, hypersalivation, tachycardia, hypotension, hypertension, weight gain, constipation, **urinary incontinence**, and fever can often be managed medically and are generally tolerated by the patient. Appropriate management of clozapine side effects facilitates a maximization of the benefits of clozapine treatment, and physicians and patients alike should be aware that there is a range of benefits to clozapine use that is wider than its risks.

3) Int Clin Psychopharmacol. 1994 Sep;9(3):207-9.

Clozapine and urinary incontinence.

Warner JP, Harvey CA, Barnes TR.

Academic Department of Psychiatry, Royal Free Hospital, London, UK.

Urinary incontinence may occur in patients with severe mental illness. Psychosis and neuroleptic medication have both been implicated, but there has been a lack of systematic evaluation of the precise relationship between these phenomena. **Incontinence has been recognized as a complication of clozapine treatment** and we examined this in 16 consecutively treated patients. Thirteen were established on therapeutic doses, one of whom was excluded from further study due to pre-existing incontinence. Retrospective assessment revealed that nocturnal incontinence was experienced by five of the remaining 12 patients, occurring in the first 3 months of treatment and resolving spontaneously in all cases. Incontinence was documented in the case notes in only one of the five cases and there was a tendency for affected patients to be embarrassed and reluctant to report it to staff. Specific enquiry may be necessary to elicit this phenomenon and **incontinence should be considered as a possible factor in poor compliance with clozapine.**

4) J Clin Psychiatry. 1996 Nov;57(11):514-8.

Clozapine-induced urinary incontinence: incidence and treatment with ephedrine.

Fuller MA, Borovicka MC, Jaskiw GE, Simon MR, Kwon K, Konicki PE.

Department of Veterans Affairs Medical Center, Cleveland, Ohio, USA.

BACKGROUND: **Treatment with the atypical antipsychotic drug clozapine appears to be associated with an increased incidence of urinary incontinence (UI).** We posited that the potent anti-alpha-adrenergic effects of clozapine were involved, and hence that an alpha-adrenergic agonist would reduce UI. We tested this hypothesis by using ephedrine, an approved alpha-adrenergic agonist. METHOD: Fifty-seven inpatients with schizophrenia or schizoaffective disorder (DSM-IV) who met the Kane criteria for being treatment refractory were treated with clozapine (75-900 mg/day). Patients who developed UI were then openly treated with ephedrine in increasing doses until UI was attenuated or a dose of 150 mg/day was attained. RESULTS: Seventeen patients developed UI as evidenced by either urine-stained sheets/clothing or direct patient reports. In 2 cases, the UI was sufficiently severe that adult diapers had to be used. Comparison of patients who developed UI and those who did not showed that UI was associated with female gender and with concomitant treatment with typical antipsychotic drugs. One patient was treated with a behavioral program, but the remaining 16 patients were treated with ephedrine. Ephedrine treatment was very effective, with 15/16 patients showing improvement within 24 hours after reaching maximum ephedrine dosage. Twelve of 16 (including the 2 most severe) eventually had a complete remission of their UI. In the remaining 4 patients, 3 had a reduction in the frequency of UI and 1 showed no response. These benefits have been maintained over the course of 12 months of subsequent treatment for several patients. There were no side effects associated with the use of ephedrine nor were there any changes in neuropsychiatric status. CONCLUSION: **Ephedrine appears to be a safe and effective treatment clozapine-associated UI. By inference, it is likely that clozapine may cause UI via its anti-alpha-adrenergic properties.**

5) Acta Psychiatr Scand. 1999 Aug;100(2):158-61.
A retrospective study of clozapine and urinary incontinence in Chinese in-patients.

Lin CC, Bai YM, Chen JY, Lin CY, Lan TH.

Department of Psychiatry, Yu-Li Veterans Hospital, Hualien, Taiwan.

OBJECTIVE: **This study investigated the incidence of clozapine-associated urinary incontinence (UI) in schizophrenic patients, the percentage of these patients with persistent urinary incontinence (PUI), and the possible factors affecting the occurrence of UI.** METHOD: A total of 61 Chinese in-patients with schizophrenia (according to DSM-IV) treated with clozapine for more than 3 months were assessed retrospectively for the occurrence of UI. Patients who still had UI at the time of assessment were classified as having PUI. Patients whose UI had resolved at the time of assessment were classified as having self-limited urinary incontinence (SUI). We compared the characteristics of UI and non-UI cases and of PUI and SUI cases. RESULTS: The results showed that urinary incontinence developed at some time in 27 of 61 patients (44.3%), and that it was persistent in 15 of 61 patients (25%). There were no statistically significant differences in age, sex, clozapine dose, duration of clozapine use, duration of index admission, duration of illness, age at onset of schizophrenia, or concurrent treatment with other psychiatric medications between the UI and non-UI groups and between the PUI and SUI groups. CONCLUSION: **Clozapine-associated urinary incontinence may be persistent in some patients, and it should be cautiously monitored in every patient taking clozapine.**